UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

[redacted]

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 11, 2009

MEMORANDUM

SUBJECT: Mutagenicity Hazard Review of P09-291

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5/11/09

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I. CONCLUSION

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The PMN is not a gene mutagen in two species of prokaryotes either without or with activation, and is a weak chromosomal mutagen in mammalian cells *in vitro* with activation but not without. There is weak concern for mutagenicity of the PMN. This weak mutagenicity concern does not reduce concern for carcinogenicity based upon other (non-genotoxicity) data, should such concern exist.

II. STRUCTURES OF P09-291 AND ANALOGUE

[redacted]

P09-291

[redacted]

III. BASIS FOR THE CONCLUSIONS

Mutagenicity data were provided with the Premanufacturing Notice on P09-291 [redacted]. These data are reviewed below.

I. Bacterial reverse mutation

P09-291 was tested in a bacterial reverse mutation assay, as reported in "Bacterial reverse mutation test of [redacted], conducted by [redacted] dated November 4, 2008. The test material [redacted] was identified as [redacted]. It was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and in *Escherichia coli* strain WP2*uvrA*, both

without and with metabolic activation using phenobarbital- and 5,6-benzoflavone-induced Sprague-Dawley rat liver S9. It was tested in a preliminary test at seven dose levels ranging from 1.22 to 5,000 µg/plate. Two independent repeats were conducted at six dose levels of 156, 313, 625, 1,250, 2,500 and 5,000 µg/plate. Both repeats were conducted in triplicate plates. Bacterial growth was inhibited at dose levels of 2,500 µg/plate and above. Dose selection was acceptable. The chemical did not induce significant increases in gene mutations under any test condition. Concurrent negative (the solvent, dimethyl sulfoxide) and positive controls produced appropriate responses.

II. *In vitro* chromosome aberration

The PMN also was tested in an *in vitro* mammalian chromosome aberration assay, as reported in "Chromosome aberration study [redacted] in cultured mammalian cells", conducted by [redacted], dated October 29, 2008. The test material was identified as for the bacterial test, with purity as above. It was tested in Chinese hamster lung CHL/IU cells both without and with metabolic activation using rat liver S9, as above. A range-finding study at eight dose levels was conducted at dose levels from 39.1 to 5,000 µg/ml. Cytotoxicity was noted at dose levels of 1,400 µg/ml and above; 1,400 µg/ml was the highest dose employed in the subsequent mutagenicity assay proper. Duplicate flasks were used for each treatment group. Cells were exposed for six hours with 18h recovery, without and with activation, to dose levels of 1,000, 1,2000 and 1,400 µg/ml. Dose selection was acceptable. Increases in structural aberrations were noted for the highest dose without activation (10.5%), and for the medium (6.0%) and highest (17.0%) doses with activation. The highest dose in both activation conditions displayed approximately 65-67% cytotoxicity. The testing laboratory considered these three responses for structural aberrations to be positive. There were no significant increases in numerical aberrations (polyploidy). Concurrent negative (saline) and positive controls (mitomycin C and benzo[a]pyrene for non-activated and activated assays, respectively) produced appropriate responses. Since only one noncytotoxic dose produced mutagenicity (medium with activation, 6% aberrations), RAD concludes that the PMN is a weak chromosome mutagen in mammalian cells *in vitro* under the conditions tested.

In summary, P09-291 is not a gene mutagen in two species of prokaryotes either without or with activation, and is a weak chromosomal mutagen in mammalian cells *in vitro* with but not without activation.

Mutagenicity data also are available on analogues of the PMN:

(1) Data on a test material that is a [redacted] indicates that it is not a gene mutagen without or with activation in *Salmonella typhimurium* stains TA98, TA100, TA1535 and TA1537, or in *Escherichia coli* strain WP2*uvrA* [redacted]

(2) Similarly, mutagenicity data [redacted] indicate that it is not a gene mutagen without or with activation in *Salmonella typhimurium* stains TA98, TA100, TA1535 and

TA1537, or in *Escherichia coli* strain WP2*uvrA,* as reviewed at the SAT meeting for that case [redacted]

The PMN is not a gene mutagen in two species of prokaryotes either without or with activation. It is a weak chromosomal mutagen in mammalian cells *in vitro* with but not without activation. There is slight concern for the mutagenicity of the PMN. There is no other basis for a mutagenicity concern for [redacted] analogues. This weak mutagenicity concern does not reduce concern for carcinogenicity based upon other (non-genotoxicity) data, should such concern exist.

III. REFERENCES

[redacted]